UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/662,783	09/12/2000	Richard A. Shimkets	15966-577 (CURA-77)	3145

30623 7590 09/09/2004

MINTZ, LEVIN, COHN, FERRIS, GLOVSKY
AND POPEO, P.C.
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
JIANG, DONG	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/662,783	SHIMKETS ET AL.	
	Examiner	Art Unit	
	Dong Jiang	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 66-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, and 66-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED OFFICE ACTION

The request filed on 13 July 2004 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/662,783 is acceptable, and a RCE has been established. An action on the RCE follows.

Applicant's amendment filed on 13 July 2004 is acknowledged and entered. Following the amendment, claim 40 is canceled, claims 1, 2 and 66 are amended, and the new claims 69-71 are added.

Currently, claims 1, 2, and 66-71 are pending and under consideration.

Declaration

The declaration filed under 37 CFR 1.132 has been considered but is ineffective to overcome the prior art reference by Gilbert et al. for the reasons addressed below under "***Rejections Over Prior Art***".

Formal Matters:

Claims 66, 70 and 71 are objected to for the following informalities, appropriate correction is required:

Claim 66, line 5, the SEQ ID NO: number is missing.

Claim 70, line 1, the recitation of "two peptides fragments" should be "two peptide fragments".

Claim 71, line 1 recites the limitation "the composition of claims 1, 2, 66, 69 *or* 70 " should be "the composition of claim 1, 2, 66, 69 or 70 ".

Objections and Rejections under 35 U.S.C. 112:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 66 and 71 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants have not pointed out, nor can the Examiner locate, the basis in the specification for newly added limitation of the peptide fragment consisting of residues 249-370 of SEQ ID NO:2 in claims 2, 66 and 71, and the limitation of "wherein a V5 *or* His6 tag, ..., is attached" in claim 71. The specification teaches *both* V5 *and* His6 tag are attached to the molecule.

This is a **new matter** rejection.

Claims 1, 2, 66-69 and 71 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited in scope to a polypeptide dimer comprising two fragments of 247-370 or 249-370 of SEQ ID NO:2, does not reasonably provide enablement for claims to a polypeptide dimer comprising two fragments of 247-370 and 247-338 of SEQ ID NO:2; 247-370 and 339-370 of SEQ ID NO:2; 247-338 of SEQ ID NO:2; or 339-370 of SEQ ID NO:2; or any other possible combinations. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Claims 1, 2, 66-69 and 71 are directed to a polypeptide dimer or the composition thereof, which, as written, read on homodimers of fragment of 247-370, 247-338, or 339-370 of SEQ ID NO:2, as well as heterodimers of various combinations, such as dimers between 247-370 and 247-338, and between 247-370 and 339-370 of SEQ ID NO:2. The specification merely discloses one type of dimer with growth-promoting activity, the p35 protein, which comprises fragment of 247-370 of SEQ ID NO:2. Although three bands are generated under reducing

conditions, bands II and III (247-338 and 339-370 of SEQ ID NO:2) turn out to be the cleaved fragments of the fragment of 247-370 of SEQ ID NO:2 (band I). Therefore, no other functional dimers comprising different fragments of SEQ ID NO:2 meeting the limitations of these claims were ever identified or particularly described. Further, the specification provides no guidance or working examples to ensure that the encompassed polypeptide dimers (except 247-370 dimer) in the claims would retain the functional activity as claimed. Furthermore, as fragments of 247-338 and 339-370 of SEQ ID NO:2 represent the N- and C-ends of the one functional growth factor domain of the molecule, respectively, they would be mutually exclusive even if the entire growth factor domain were not required for the bioactivity, and it is unlikely that both would be active. Given the fact that fragments of 247-338 and 339-370 of SEQ ID NO:2 merely represent 2/3 and 1/3 of the functional growth factor domain of the molecule, it is unlikely or highly unpredictable that dimers comprising such fragments would retain the desired activity. Therefore, undue experimentation would be required to determine such.

Due to the large quantity of experimentation necessary to determine whether the polypeptide dimers as claimed (except 247-370 dimer) would retain the functional activity, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art that has not established that a polypeptide dimer comprising 339-370 of SEQ ID NO:2, for example, would retain the biological activity, the unpredictability, and the breadth of the claims which embrace polypeptide dimers with various combinations of the three fragments of SEQ ID NO:2, undue experimentation would be required of the skilled artisan to use the claimed invention in its full scope.

Claims 70 and 71 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 70 and 71 are directed to a functional polypeptide dimer comprising, as the first peptide, 16 kDa or 5-6 kDa fragment of SEQ ID NO:2, and the second peptide, 22-25 kDa fragment of SEQ ID NO:2. The specification merely discloses one fragment of SEQ ID NO:2

for each molecular weight with particularity, i.e., fragment of 247-370 (22-25 kDa), 247-338 (16 kDa), or 339-370 (5-6 kDa), and no other fragments of SEQ ID NO:2 meeting the limitations of these claims were ever identified or particularly described. Therefore, one of skilled in the art would not know how to make a number of species that would be commensurate in scope with the claims. Further, as addressed above, dimers comprising fragments that merely have a partial sequence (for example, 1/3) of the functional domain are highly unlikely to retain the desired activity, and the specification fails to provide guidance or working example regarding such. Therefore, for the same reasons above, undue experimentation would be required to make and/or use the claimed invention in its full scope.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, and 66-71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "*the bonded* polypeptide " in lines 3-4. There is insufficient antecedent basis for this limitation in the claim. The claim is further indefinite for the recitation of "dimer comprising *at least two* peptides" because the term "dimer", by definition, comprises two elements, and therefore, "at least two" is not needed. The claim is further indefinite and confusing for the recitation of "dimer comprising at least two *peptides* selected from the group consisting of ..., and the bonded *polypeptide* composed of ..." because it is not clear which is the *first* peptide, and which is the *second* peptide. The claim is further indefinite for the recitation of "the bonded polypeptide *composed of*" because it is unclear what is intended by "composed of", and the metes and bounds of the claim, therefore, cannot be determined. The claim is further indefinite for the recitation of "*said polypeptide* has a growth factor activity" because it is unclear which polypeptide it refers to, as there are two "polypeptide" in the claim: the polypeptide dimer and the bonded polypeptide.

Claim 2 is indefinite for the recitation of "wherein the polypeptide has ..." because it is unclear to what it refers. "Wherein the polypeptide *dimer* has ..." is suggested. Further, the claim

recites "a composition", which usually comprises more than one ingredient. However, only one ingredient is indicated in the claim, "isolated polypeptide dimers".

Claim 66 is indefinite because it is unclear whether "isolated polypeptide dimers" in line 1 are the same as or equal to "a protein of 35 kDa" in line 5. The claim is further indefinite because it is unclear which fragments are associated with each other as not any random combination of two fragments would make a protein of 35 kDa. Furthermore, the claim recites "a composition", which usually comprises more than one ingredient. However, only one ingredient is indicated in the claim, "isolated polypeptide dimers".

Claim 67 is indefinite because it is unclear to what "*a polypeptide* of claim 2" refers. "*The* polypeptide *dimer* of claim 2" is suggest if that is intended. Claim 68 is similarly indefinite.

Claim 69 is indefinite because it is unclear how the two peptides are associated to form a polypeptide, and which one is the first peptide, and which one is the second peptide. The claim is further indefinite for the recitation of "at least two", and "composed of" for the same reasons above.

Claim 70 is indefinite for the recitation of "at least two" for the same reasons above.

Claim 71 recites the limitation "*the composition* of claims 1, 2, 66, 69 or 70 " in line 1. There is insufficient antecedent basis for this limitation in the independent claims 1, 69 and 70.

The remaining claims are rejected for depending from an indefinite claim.

Rejections Over Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1, 2, and 66-68 remain rejected, and the new claim 69 and 71 are rejected under 35 U.S.C. 102(e) as being anticipated by Gilbert et al., US 6,495,668 B1, for the reasons of record set forth in the last Office Actions mailed on 24 June 2003, and 13 January 2004, and for the reasons below.

Applicants declaration and argument filed on 13 July 2004 have been fully considered, but are not deemed persuasive for the reasons below.

At page 3, items 7-9 and 11-13 of the declaration, Applicants argue that the polypeptide dimers of associated peptide fragments of SEQ ID NO:2 in the pending claims, when analyzed by SDS-PAGE under non-reducing conditions yielded a 35 kDa band, and under reducing conditions three bands were detected: I, 22-25 kDa; II, 16 kDa; and III, 5-6 kDa, wherein the N-terminus of bands I and II begin at residue 247 of SEQ ID NO:2, and bands II and III are cleavage fragments of the polypeptide corresponding to band I (item 7); that applicants have not been able to find such teaching or suggestion in the Gilbert reference (item 8); that Gilbert teaches fragment of 258-370, 250-370, and 246-370, and the domain boundaries varying ± 5 residues from these N-terminal positions (item 9); and that Gilbert does not disclose the specific peptides of 247-338 and 339-370, nor a peptide dimer as claimed, and therefore, Gilbert does not recognize the claim peptide dimer (items 11-13). These arguments are not persuasive because Gilbert clearly teaches peptide dimers (claim 1, and column 7, lines 23-25), and Gilbert discloses the specific peptide dimer comprising 247-370 of the present SEQ ID NO:2 as shown in claims 1 and 6 of the patent. Gilbert teaches that each of said first and second polypeptides is from 113-118 amino acid residues in length (claim 6), that is the polypeptide fragment may start at any residue from position 233 (138 residues in length) to 258 (113 residues in length), as position 370 is the end of the C-terminus of the zvegf4 molecule. As such, Gilbert identifies 26 specific polypeptide fragments and dimers thereof, including a polypeptide dimer comprising residues 247-370 of the present SEQ ID NO:2. The presently claimed peptide dimer, as written, read on a peptide dimer comprising fragments of 247-370 of SEQ ID NO:2. With respect to the fragments of 247-338 and 339-370 of SEQ ID NO:2, the total residues of the two fragments are identical to that of the fragment of 247-370 of SEQ ID NO:2, and there is no evidence that the fragment of 247-370 is cleaved into the two fragments under its functional stage (non-reducing condition). Further, if the presently claimed dimmer generate three bands under reducing conditions, Gilbert's polypeptide dimer would do the same under the same condition because as it comprises identical peptide fragments as that of the instant invention (corresponding to 247-370 of SEQ ID NO:2), and it would have been an inherent property for the same molecule. Therefore, the reference anticipates the present claims. With respect to the other claimed peptide dimers

comprising fragments of 247-338 and 339-370 separately, they are not enabled for the reasons below under *Objections and Rejections under 35 U.S.C. 112.*

At pages 3 and 4, items 10 and 14 of the declaration, Applicant argues that it is applicants opinion that it is not possible to predict which of the many peptides encompassed by the teaching of Gilbert (residues 246-370 $\pm$5) would have the bioactivity as that of the present claims (item 10); that there are multiple factors involved in generating a bioactive PDGF-D peptide dimer, that the ordinarily skilled artisan would not have a reasonable expectation of success in predicting whether any particular PDGF-D peptide dimer would be bioactive based solely on its sequence; and that minor changes at either terminus may have significant effects on dimerization, aggregation, expression and bioactivity (item 14). This argument is not persuasive because it is irrelevant whether any or all of Gilbert's fragments would be able to form bioactive dimers because of the simple fact that Gilbert teaches, among other fragments, the fragment of 247-370 of SEQ ID NO:2 of the instant claims and the dimer thereof, and therefore, the prior art reference anticipates the instant claims. The issue is not the matter of "a reasonable expectation of success in predicting", or predictability, rather, the issue is that the prior art reference teaches what is claimed in the present invention, and therefore anticipates the claims. Further, *even if* the argument were relevant, it would not be persuasive for the following reasons: first, it is largely opinion only, and presents no further scientific support, nor valid data to prove that any of Gilbert's fragments would not have bioactivity. Second, Gilbert's peptide dimer are not just *any* particular PDGF-D peptide dimer, rather, they represent peptide dimer comprising only the functional growth factor domain of the molecule, with possible extension of a few amino acids at the N-terminus. Therefore, such argument is void. Furthermore, with respect to the argument that minor changes at either terminus may have significant effects on the molecule, the fragments of 247-338 and 339-370 of SEQ ID NO:2 in the present invention, which merely represent 2/3 and 1/3 of the functional growth factor domain respectively, cannot be considered "*minor*" changes by any measurement or in comparison to Gilbert's fragments, each of which comprises the complete functional fragment of the growth factor domain, residues 258-370, and has merely difference in a few amino acids at the N-terminus. Therefore, a person of ordinary skill in the art would accept that Gilbert's peptide dimer

comprising the complete functional growth factor domain of the molecule would be functional. Therefore, in the absence of any additional evidence, mere opinion by applicants is ineffective to overcome the teachings of the prior art reference.

At pages 4-6 of the response, applicants present the same arguments as that in the declaration. Applicants arguments have been fully considered, but they are not deemed persuasive for the same reasons above.

With respect to the limitation of "wherein a V5 or His6 tag, or both, is attached at residue 370" in the new claim 71, Gilbert teaches that polypeptides of the invention can be prepared with changes that do not significantly affect the folding or activity of the protein or polypeptide, and include an amino- or carboxyl terminal affinity tag (column 14, lines 29-40), such as a 6-residue polyhistidine tag (column 15, lines 6-18). The reference, therefore, also anticipates claim 71.

Conclusion:

No claim is allowed.

Advisory Information:

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 571-272-0872. The examiner can normally be reached on Monday - Friday from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Dong Jiang, Ph.D.
Patent Examiner
AU1646
8/26/04

JANET ANDRES
PRIMARY EXAMINER